drug delivery depends on a variety of factors, some of which can be controlled by the clinician or scientist and others that are uncontrollable. Uncontrollable factors include, among others, the airway geometry of the patient's respiratory tract and lung and other respiratory diseases. Of the controllable factors, two are of particular interest. The first is the droplet size and droplet size distribution. The second is the breathing pattern.

A major factor governing the effectiveness of drug deposition in the lungs is the size of the inspired particles. Depending on the particle size, total deposition in various regions of the lung may vary from 11% to 98%. See Heyder et al., Aerosol Sci., 1986, 17, 811-825, the disclosure of which is herein incorporated by reference. Therefore, proper selection of particle size provides a way to target liquid droplets to a desired lung region. It is particularly difficult, however, to generate a liquid spray in which all the droplets will have the same size or the same aerodynamic behavior such that drug deposition in the desirable lung region is predictable.

A parameter that may be used to define droplet size is the respirable fraction (RF). The respirable fraction (RF) is defined as the fraction of the mass of aerosol droplets falling between a particular size range, usually in the range from about 1 μm to 6 μm. See D.C. Cipolla, et al., Assessment of Aerosol Delivery Systems for Recombinant Human Deoxyribonuclease, S.T.P. Pharma Sciences 4(1) 50-62, 1994, the disclosure of which is herein incorporated by reference. As used hereinafter, the term respirable fraction (RF) will include the percentage of droplets having sizes falling in the range of from about 1 μm to 6 μm. Another parameter that may be used to evaluate nebulization performance is the efficiency (E). The efficiency (E) of a nebulizer is the amount of liquid which is actually aerosolized and leaves the nebulizer in aerosolized form as compared to the amount of liquid that is initially supplied to the nebulizer. See D.C. Cipolla, et al., Assessment of Aerosol Delivery Systems for Recombinant Human Deoxyribonuclease, S.T.P. Pharma Sciences 4(1) 50-62, 1994. Still another parameter that may be used to measure the performance of nebulizers is the delivery percentage (D) which is the respirable fraction (RF) multiplied by the efficiency (E) . See D.C. Cipolla, et al., Assessment of Aerosol Delivery Systems for Recombinant Human

Deoxyribonuclease, S.T.P. Pharma Sciences 4(1) 50-62, 1994.

A variety of inhalation devices have been proposed including air jet nebulizers, ultrasonic nebulizers, and metered dose inhalers (MDIs). Air jet nebulizers usually utilize a high pressure air compressor and a baffle system that separates the small particles from the spray. Ultrasonic nebulizers generate ultrasonic waves with an oscillating piezoelectric crystal to produce liquid droplets. Another type of ultrasonic nebulizer of interest is described in U.S. Pat. Nos. 5,261,601 and 4,533,082. This nebulizer includes a housing that defines a chamber for holding a quantity of liquid to be dispensed. A perforated membrane is held over the chamber and defines a front wall of the chamber, with the rear surface of the membrane being in constant contact with the reservoir of liquid held in the chamber. The apparatus further includes an ultrasonic vibrator connected to the housing to vibrate the perforated membrane. Typical MDIs usually employ a gas propellant, such as CFC, which carries the therapeutic substance and is sprayed into the mouth of the patient.

Most commercially available inhalers produce sprays having a respirable fraction (RF) of 80% or less, with ultrasonic nebulizers usually having a respirable fraction (RF) of less than about 50%, thereby making dosing control difficult and inaccurate. Presently, most commercially available inhalers also have a poor efficiency (E), usually less than about 60%. See D.C. Cipolla, et al., Assessment of Aerosol Delivery Systems for Recombinant Human Deoxyribonuclease, S.T.P. Pharma Sciences 4(1) 50-62, 1994. Such inefficiency often results from the construction of the nebulizer since a certain amount cannot be nebulized and remains within the device. Since most commercially available nebulizers have both a poor respirable fraction (RF) and a poor efficiency (E), the delivery percentage (D) is also poor. Therefore, such inhalers have generally not been used for delivery of drugs that have potent therapeutic agents such as hormones and peptides or other drugs having a high level of toxicity and which can be expensive. --

Please add after the text on page 7, line 2, the text below, which is from U.S. Patent No. 5,586,550 (at col. 3, line 38 to col. 4, line 29), which patent was incorporated by reference into the present application.

-- Preferably, the apertures will be configured to eject liquid droplets having a respirable fraction (RF) of greater than about 70%, preferably more than about 80%, and most preferably more than about 90%. In another preferable aspect, the apparatus will have an efficiency (E) at or closely approaching 100%, i.e. substantially all liquid supplied to the rear surface will be aerosolized and will be available for inhalation. In this way, the delivery percentage (D) will usually be about the same as the respirable fraction (RF), i.e. greater than about 70%.

C2

In one exemplary aspect, the size of the apertures at the front surface is in the range from about 1 μm to 6 μm, with the apertures have a slope at the front surface of about 10° or greater relative to a central axis of the apertures, preferably being in the range from about 10° to 20° relative to the central axis of the apertures, and more preferably being in the range from about 10° to 15° relative to the central axis. Preferably, the thin shell member will have a thickness of about 50 μm to about 100 μm, more preferably from about 75 μm to about 100 μm which provides the thin shell member with sufficient rigidity to vibrate in unison and provides sufficient aperture volume. In the present invention, ejection of droplets is developed due to the solid/fluid interaction inside the aperture, i.e. the interaction of the liquid against the tapered wall of the aperture. The cross sectional geometry of the aperture is therefore important. For example, if the aperture has a straight cylindrical wall with a slope of 0° relative to the central axis (or a 90° slope relative to the front surface of the thin shell member), ejection will not occur. Instead, the vibratory motion will cause the liquid to break loose from the vibratory surface so that it will not eject through the aperture.

For apertures smaller than 6 μm, the slope near the exit opening of the aperture is particularly important because the discharge coefficient of such an aperture is substantially smaller than for larger apertures. For apertures smaller than 6 μm, a slight

variation in the slope near the small opening of the aperture will make significant influence on ejection of droplets because the tapered shape near the opening increases the surface area that is subjected to solid/fluid interaction near the exit opening. For example, vibration of the thin shell member when the apertures have a slope of 20° (relative to the central axis of the apertures) near the small opening produces 10 times more droplets than when the apertures are at right angles to the front surface. In this manner, a high flow rate can be achieved using a small thin shell member. --

C2

~~Please add the following text, immediately after the previous addition above, the text below, which is from U.S. Patent No. 5,586,550 (at col. 7, lines 35 to 47), which patent was incorporated by reference into the present application.~~

-- Apertures in the thin shell member of the invention will preferably be tapered in geometry, with the smaller end of the aperture being located at a front surface of the thin shell member and the larger opening of the aperture being at the rear surface of the thin shell member. The size of the apertures at the front surface will preferably be in the range from about 1 μm to 6 μm, with the slope of the apertures at the front surface being in the range from about 10° or greater relative to a central axis extending through the apertures, preferably from about 10° to 20° relative to the central axis extending through the apertures, and more preferably being in the range from about 10° to 15° relative to the central axis.–

C3 Cont.

~~Please add immediately after the previous addition above, the text below, which is from U.S. Patent No. 5,586,550 (at col. 7, line 52 to col. 9, line 3, with the figure and reference numbers renumbered), which patent was incorporated by reference into the present application~~.

-- Referring to FIG. 23, construction of the mouthpiece assembly 512 will be described. The mouthpiece assembly 512 includes an elongate tubular housing 516

having a proximal end 518 and a distal end 520. At the distal end 520 is a mouthpiece 522, while a liquid supply cartridge 524 is at the proximal end 518. As will be described in grater detail hereinafter, a carrier plate 526 extends from the housing 516 and is provided to hold a thin shell member within the housing 516. An elastomeric 0-ring 528 is placed adjacent the carrier plate 526 and is positioned against a vibrating beam as described in greater detail hereinafter. To dynamically isolate the carrier plate 526, the housing 512 is preferably constructed of an elastomeric material, preferably having a modulus of elasticity of about 100 psi to 150 psi.

Referring to FIG. 24, the interior of the mouthpiece assembly 512 will be described. The tubular housing 516 forms a central chamber 532 having an opening 534 at the mouthpiece 522. Annularly extending into the central chamber 532 is the carrier plate 526. In turn, the carrier plate 26 is attached about a thin shell member 536 having a front surface 538 and a rear surface 540. Extending between the front surface 538 and rear surface 540 are a plurality of tapered apertures (not shown) having the smaller opening at the front surface 538 and the larger opening at the rear surface 540. Upon vibration of the carrier plate 526, the thin shell member 536, is vibrated so that liquid may be ejected through the apertures and from the front surface 538 as described hereinafter.

An amount of liquid 542 is supplied to the rear surface 540 from the liquid supply cartridge 524. The liquid cartridge 524 includes a divider 544 that separates the liquid supply cartridge 524 into an air volume 546 and a liquid volume 548. To dispense liquid from the liquid volume 548, the liquid supply cartridge 524 is squeezed to force liquid in the liquid volume 548 through a nozzle 550 where it comes into contact with the rear surface 540 of the thin shell member 536. The cartridge 524 becomes permanently deformed when squeezed so that the liquid 542 delivered to the rear surface 540 will not be withdrawn back into the liquid volume 548. The size of the air volume 546 will be configured such that all of the liquid within the liquid volume 548 will be transferred from the liquid volume 548 when the cartridge 524 is squeezed.

The liquid 542 delivered from the supply cartridge 524 will usually be

held to the rear surface 540 solely by surface tension forces. In this way, the liquid 542 may remain in contact with the rear surface 540 until ejected and without the need for a separate chamber to hold the liquid 542 against the rear surface 540. To eject the liquid 542 from the front surface 538, the carrier plate 526 is vibrated to in turn vibrate the thin shell member 36. The liquid 542 adhering to the rear surface then passes through the apertures and from the front surface 538 as described in U.S. Pat. No. 5,164,740 and copending application Ser. Nos. 08/163,850 and 08/417,311, the entire disclosures of which are herein incorporated by reference.

C2

The thin shell member 536 is preferably formed of a thin, rigid material having a hemispherical geometry. Alternatively, the thin shell member 536 may be parabolic, arc shaped, or curved in geometry. The thin shell member 536 will have a very high bending stiffness which will allow it to follow the vibratory motion of the carrier plate 526 as a rigid body. In this way, the entire thin shell member 536 will vibrate in unison so that all apertures are subject to the same amplitude of vibration. Such vibration will assist in ejecting uniformly sized droplets (i.e. having a respirable fraction (RF) of greater than about 70%, preferably more than about 80%, and most preferably more than about 90%) simultaneously from most or all of the apertures. The spray produced by the thin shell member 536 is dispensed into the central chamber 532 in the direction of the opening 534. In this manner, as the patient inhales from the mouthpiece 522, the spray within the central chamber 532 will be drawn into the patient's lungs.

To control the time and/or rate at which the spray is produced, the mouthpiece assembly 512 further includes an acoustic chamber 552 having holes 554 and 556. Upon inhalation, air within the central chamber 532 passes through the holes 554 and 556 to produce an acoustic tone. This tone may be detected as described in greater detail hereinafter and used to determine both when the patient is inhaling and the patient's inspiratory flow rate. Such a signal may then be used to actuate the oscillating assembly which vibrates the thin shell member 536. Such a signal may be employed to control the time at which the shell member 536 is vibrated, e.g., such as only during inhalation.

C2 Alternatively, such a signal may also be employed to vibrate the thin shell member 536 at a frequency corresponding to the inspiratory flow rate. --

Please add after the text ending at page 23, line 13 of the present application, the text below, which is from U.S. Patent No. 5,586,550 (at col. 7, line 52 to col. 9, line 3), which patent was incorporated by reference into the present application.

--Referring to FIG. 23, construction of the mouthpiece assembly 512 will be described. The mouthpiece assembly 512 includes an elongate tubular housing 516 having a proximal end 518 and a distal end 520. At the distal end 520 is a mouthpiece C3 522, while a liquid supply cartridge 524 is at the proximal end 518. As will be described in grater detail hereinafter, a carrier plate 526 extends from the housing 516 and is provided to hold a thin shell member within the housing 516. An elastomeric 0-ring 528 is placed adjacent the carrier plate 526 and is positioned against a vibrating beam as described in greater detail hereinafter. To dynamically isolate the carrier plate 526, the housing 512 is preferably constructed of an elastomeric material, preferably having a modulus of elasticity of about 100 psi to 150 psi.

Referring to FIG. 24, the interior of the mouthpiece assembly 512 will be described. The tubular housing 516 forms a central chamber 532 having an opening 534 at the mouthpiece 522. Annularly extending into the central chamber 532 is the carrier plate 526. In turn, the carrier plate 526 is attached about a thin shell member 536 having a front surface 538 and a rear surface 540. Extending between the front surface 538 and rear surface 540 are a plurality of tapered apertures (not shown) having the smaller opening at the front surface 538 and the larger opening at the rear surface 540. Upon vibration of the carrier plate 526, the thin shell member 536, is vibrated so that liquid may be ejected through the apertures and from the front surface 538 as described hereinafter.

An amount of liquid 542 is supplied to the rear surface 540 from the liquid supply cartridge 524. The liquid cartridge 524 includes a divider 544 that separates the liquid supply cartridge 524 into an air volume 546 and a liquid volume 548. To dispense

liquid from the liquid volume 548, the liquid supply cartridge 524 is squeezed to force liquid in the liquid volume 548 through a nozzle 550 where it comes into contact with the rear surface 540 of the thin shell member 536. The cartridge 524 becomes permanently deformed when squeezed so that the liquid 542 delivered to the rear surface 540 will not be withdrawn back into the liquid volume 548. The size of the air volume 546 will be configured such that all of the liquid within the liquid volume 548 will be transferred from the liquid volume 548 when the cartridge 524 is squeezed.

C3 Cont.

The liquid 542 delivered from the supply cartridge 524 will usually be held to the rear surface 540 solely by surface tension forces. In this way, the liquid 542 may remain in contact with the rear surface 540 until ejected and without the need for a separate chamber to hold the liquid 542 against the rear surface 540. To eject the liquid 542 from the front surface 538, the carrier plate 526 is vibrated to in turn vibrate the thin shell member 536. The liquid 542 adhering to the rear surface then passes through the apertures and from the front surface 538 as described in U.S. Pat. No. 5,164,740 and copending application Ser. Nos. 08/163,850 and 08/417,311, the entire disclosures of which are herein incorporated by reference.

The thin shell member 536 is preferably formed of a thin, rigid material having a hemispherical geometry. Alternatively, the thin shell member 536 may be parabolic, arc shaped, or curved in geometry. The thin shell member 536 will have a very high bending stiffness which will allow it to follow the vibratory motion of the carrier plate 526 as a rigid body. In this way, the entire thin shell member 536 will vibrate in unison so that all apertures are subject to the same amplitude of vibration. Such vibration will assist in ejecting uniformly sized droplets (i.e. having a respirable fraction (RF) of greater than about 70%, preferably more than about 80%, and most preferably more than about 90%) simultaneously from most or all of the apertures. The spray produced by the thin shell member 536 is dispensed into the central chamber 532 in the direction of the opening 534. In this manner, as the patient inhales from the mouthpiece 522, the spray within the central chamber 532 will be drawn into the patient's lungs.

To control the time and/or rate at which the spray is produced, the